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0026611.4 31 October 2000 (31.10.2000) GB(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH];
124, Grenzacherstrasse, CH-4070 Basle (CH).(72) Inventors: DEVOS, Rene; 4 Salmon Close, Welwyn
Garden City, Hertfordshire AL7 1TR (GB). DYMICK,

Brian, William; 15 Vesta Avenue, St. Albans, Hertfordshire AL1 2PJ (GB). HOBBS, Christopher, John; 9 Magnolia Close, Hertford, Hertfordshire SG13 7UR (GB). JIANG, Wen-Rong; 20 Salmon Close, Welwyn Garden City, Hertfordshire AL7 1TR (GB). MARTIN, Joseph, Armstrong; 10 The Chownes, West Common, Harpenden, Herts AL5 2BN (GB). MERRETT, John, Herbert; 23 Bush Spring, Baldock, Hertfordshire SG7 6QT (GB). NAJERA, Isabel; 49 Salisbury Avenue, St. Albans, Hertfordshire AL1 4TZ (GB). SHIMMA, Nobuo; Higashikaigan-Minami 2-11-19, Chigasaki-shi, Kanagawa-ken 253-0054 (JP). TSUKUDA, Takuo; 540-22 Rensyoji, Odawara-shi, Kanagawa-ken 250-0865 (JP).

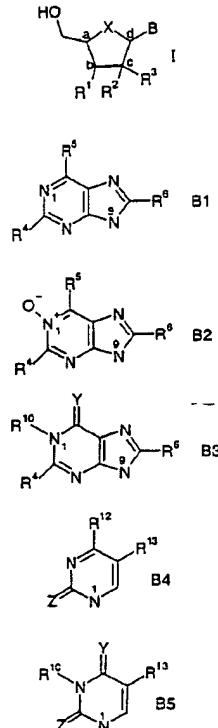
(74) Agent: RAUBER, Beat; 124 Grenzacherstrasse, CH-4070 Basle (CII).

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[Continued on next page]

(54) Title: NUCLEOSIDE DERIVATIVES FOR THE TREATMENT OF HEPATITIS C

Use of compounds of formula I



(57) **Abstract:** Use of compounds of formula (I), wherein R¹ is hydrogen, hydroxy, alkyl, hydroxalkyl, alkoxy, halogen, cyano, isocyano or azido; R² is hydrogen, hydroxy, alkoxy, chlorine, bromine or iodine; R³ is hydrogen; or R² and R³ together represent =C(H)₂; or R² and R³ represent fluorine; X is O, S or CH₂; a, b, c, d denoting asymmetric carbon atoms each of which is substituted with 4 different substituents; and B signifies a purine base B1 which is connected through the 9-nitrogen of formula (B1), wherein R⁴ is hydrogen, hydroxyl, alkyl, alkoxy, alkylthio, aryloxy, arylthio, heterocyclyl, NR⁷R⁸, halogen or SH; R⁵ is hydrogen, hydroxy, alkyl, haloalkyl, cycloalkyl, alkoxy, alkylthio, aryl, aryloxy, heterocyclyl, heterocyclamino, halogen, NR⁷R⁸, NHOR⁹, NHNR⁷R⁸ or SH; R⁶ is hydrogen, hydroxy, alkyl, alkoxy, alkylthio, aryloxy, arylthio, heterocyclyl, NR⁷R⁸, halogen, SH or cyano; R⁷ and R⁸ are independently of each other hydrogen, alkyl, aryl, hydroxalkyl, alkenylalkyl, alkynylalkyl, cycloalkyl or acyl; R⁹ is hydrogen, alkyl or aryl; or B signifies an oxidised purine base B2 which is connected through the 9-nitrogen of formula (B2), wherein R⁴, R⁵ and R⁶ are as defined above; or B signifies a purine base B3 which is connected through the 9-nitrogen of formula (B3), wherein R⁴ and R⁶ are as defined above; R¹⁰ is hydrogen, alkyl or aryl; Y is O, S or NR¹¹; R¹¹ is hydrogen, hydroxy, alkyl, OR⁹, heterocyclyl or NR⁷R⁸; R⁷, R⁸ and R⁹ are as defined above; or B signifies a pyrimidine base B4 which is connected through the 1-nitrogen of formula (B4), wherein Z is O or S; R¹² is hydrogen, hydroxy, alkyl, alkoxy, haloalkyl, alkylthio, aryl, aryloxy, arylthio, heterocyclyl, heterocyclamino, halogen, NR⁷R⁸, NHOR⁹, NHNR⁷R⁸ or SH; R¹³ is hydrogen, alkyl, hydroxalkyl, alkoxyalkyl, haloalkyl, cycloalkyl or halogen; R⁷, R⁸ and R⁹ are as defined above; or B signifies a pyrimidine base B5 which is connected through the 1-nitrogen of formula (B5), wherein Y, Z, R¹⁰ are as defined above for the treatment of diseases mediated by the Hepatitis C Virus (HCV) or for the preparation of a medicament for such treatment. The invention is concerned with novel and known purine and pyrimidine nucleoside derivatives, their use as inhibitors of subgenomic Hepatitis C Virus (HCV) RNA replication and pharmaceutical compositions of such compounds.

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CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

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CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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14 November 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07H19/06 C07H19/16 A61K31/7064 A61K31/7076 A61P31/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHEDMinimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 01443 A (WELLCOME FOUND ; KOSZALKA GEORGE WALTER (US); DRAANEN NANINE AGNETA) 20 January 1994 (1994-01-20) examples claims page 3, paragraph 3 —	1, 2, 5, 6, 8
X	WO 98 16184 A (ICN PHARMACEUTICALS ; AVERTT DEVERON (US); TAM ROBERT (US); WANG GU) 23 April 1998 (1998-04-23) examples claims page 11, line 14 —	1, 15, 16 —/—

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

5 July 2002

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

de Nooy, A

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 01/09633

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 55 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.
2. Claims Nos.: 43, 49–57 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,
no additional fees are to be refunded.

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 43,49-57 (all partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty for claim 43. So many documents were retrieved that it is impossible to determine which parts of the claim may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, it appears impossible to execute a meaningful search and/or to issue a complete search report over the whole breadth of the claims. Consequently, the search and the report for this claim has been restricted to the case where R13'''' is an alkyl but not methyl.

Present claims 49-57 relate to an extremely large number of compounds. In fact, the claims contain so many options, that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the above mentioned claims have been searched insofar as the compounds of claim 49 fall within earlier compound claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 (in part), 3-4 (in part), 12-13 (in part), 14, 34, 35, 50-56 (in part)

Compounds of Formula I-a of claim 34 where B' = B2-a of claim 34, and uses, compositions and processes pertaining thereto.

2. Claims: 1 (in part), 3-4 (in part), 15-16 (in part), 17, 36, 37, 50-56 (in part)

Compounds of Formula I-b of claim 36 where B'' = B3-a of claim 36, and uses, compositions and processes pertaining thereto.

3. Claims: 1-4 (in part), 18-25 (in part), 26, 27-28 (in part), 29, 38-42, 50-56 (in part)

Compounds of Formula I-c of claim 38 where B''' = B4-a of claim 38, compounds of Formula I-d of claim 40 where B'''' = B4-b of claim 40 or 41, and uses, compositions and processes pertaining thereto.

4. Claims: 1-4 (in part), 30-32 (in part), 33, 43-48, 50-56 (in part)

Compounds of Formula I-e of claim 43 where B''''' = B5-a of claim 43, compounds of Formula I-f of claim 45 where B'''''' = B5-b of claim 45, compounds of Formula I-g of claim 47 where B''''''' = B5-c of claim 47 and uses, compositions and processes pertaining thereto.

5. Claims: 1-4 (in part), 5-10, 12-13 (in part), 15-16 (in part), 18-25 (in part), 27-28 (in part), 30-32 (in part), 55-56 (in part)

Use of compounds of the above mentioned claims which do not fall within one of the previous subjects for the treatment of Hepatitis C Virus or for the preparation of a medicament for such treatment.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/09633

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 05687 A (UNIV BIRMINGHAM ;WELLCOME FOUND (GB); MILLER JOHN ALLEN (GB); YOUN) 17 March 1994 (1994-03-17) examples claims page 4, line 22 - line 36 ---	1,2, 30-32
A	EP 0 468 352 A (NIPPON KAYAKU KK) 29 January 1992 (1992-01-29) examples claims page 14, line 17 ---	1
X	US 5 102 873 A (MONTGOMERY JOHN A ET AL) 7 April 1992 (1992-04-07) example 3 ---	34
X	US 4 755 594 A (BRIDGES ALEXANDER J ET AL) 5 July 1988 (1988-07-05) example 4 ---	34
X	P.J.M. VAN GALEN ET AL.: "A binding site model and structure-activity relationships for the rat A3 adenosine receptor" MOLECULAR PHARMACOLOGY, vol. 45, 1994, pages 1101-1111, XP008000722 compound 30 ---	34
A	US 5 998 387 A (SCAMMELLS PETER J ET AL) 7 December 1999 (1999-12-07) figure 2 ---	34
A	K. MIURA ET AL.: "Chemical conversion of adenine to guanosine (Nucleosides and nucleotides. XI)" CHEM. PHARM. BULL., vol. 23, 1975, pages 464-466, XP002190612 chart 1 ---	34
X	W.M. HAMMARGREN ET AL.: "Identification of a novel nucleoside, 1,N6-dimethyladenosine, in human cancer urine" ANALYTICA CHIMICA ACTA, vol. 247, 1991, pages 201-209, XP008005307 compound 1 ---	36
X	US 3 891 623 A (VORBRUGGEN HELMUT ET AL) 24 June 1975 (1975-06-24) examples 2,3 ---	38
		-/-

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/09633

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	H. VORBRÜGGEN ET AL.: "Eine neue einfache Synthese von Cytidinen" LIEBIGS ANN. CHEM., 1975, pages 988-1002, XP002204034 compound 19 —	38
X	X.-X. ZHOU ET AL.: "Pyridyl groups for protection of the imide functions of uridine and guanosine. Exploration of their displacement reactions for site-specific modifications of uracil and guanine bases" ACTA CHEMICA SCANDINAVICA B, vol. 40, 1986, pages 806-816, XP002204035 the whole document —	38
X	R.W. MILES ET AL.: "Nucleic acid related compounds. 87. Nucleophilic functionalization of cytidine and 2'-deoxycytidine derivatives via elaboration of the 4-amino group into a readily displaced 1,2,4-triazol-4-yl substituent" J. ORG. CHEM., vol. 60, 1995, pages 7066-7069, XP002204036 compounds 3,4 —	38
X	G.E. KEYSER ET AL.: "Iodomethylethers from 1,3-dioxolane and 1,3-oxothiolane: preparation of acyclic nucleoside analogs" TETRAHEDRON LETTERS, 1979, pages 3263-3264, XP002204037 compound 3 —	38
X	US 4 526 988 A (HERTEL LARRY W) 2 July 1985 (1985-07-02) the whole document —	40
X	HERTEL L W: "SYNTHESIS OF 2-DEOXY-2,2-DIFLUORO-D-RIBOSE AND 2-DEOXY-2,2-DIFLUORO-D-RIBOFURANOSYL NUCLEOSIDES" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 53, no. 11, 27 May 1988 (1988-05-27), pages 2406-2409, XP000572745 ISSN: 0022-3263 the whole document —	40
	-/-	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/09633

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHOU T S ET AL: "STEREOSPECIFIC SYNTHESIS OF 2-DEOXY-2,2-DIFLUORORIBONOLACTONE AND ITS USE IN THE PREPARATION OF 2'-DEOXY-2',2'-DIFLUORO-BETA-D-RIBOFURANOSYL PYRIMIDINE NUCLEOSIDES: THE KEY ROLE OF SELECTIVE CRYSTALLIZATION" SYNTHESIS, GEORG THIEME VERLAG. STUTTGART, DE, no. 6, 1 June 1992 (1992-06-01), pages 565-570, XP000572747 ISSN: 0039-7881 compounds 1,16	40
X	KOTRA L P ET AL: "STRUCTURE-ACTIVITY RELATIONSHIPS OF 2'-DEOXY-2',2'-DIFLUORO-L-ERYTHRO-PENTOFURANOSYL NUCLEOSIDES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 40, no. 22, 1997, pages 3635-3644, XP000867642 ISSN: 0022-2623 compounds 43-52	40
X	KOTRA L P ET AL: "Synthesis of 2,3-dideoxy-2,2-difluoro-1-glycero-pentofuranosyl nucleosides" CARBOHYDRATE RESEARCH, ELSEVIER SCIENTIFIC PUBLISHING COMPANY. AMSTERDAM, NL, vol. 306, no. 1-2, January 1998 (1998-01), pages 69-80, XP004204788 ISSN: 0008-6215 scheme 1	40
X	M. SEKINE, T. NAKANISHI: "Facile synthesis of 3'-O-methylthymidine and 3'-deoxythymidine and related deoxygenated thymidine derivative: A new method for selective deoxygenation of secondary hydroxy groups" J. ORG. CHEM., vol. 55, 1990, pages 924-928, XP002204038 compound 2	43
X	A. HAMPTON ET AL.: "Species- or Isozyme-specific enzyme inhibitors. 5. Differential effects of thymidine substituents on affinity for rat thymidine kinase isozymes" J. MED. CHEM., vol. 25, 1982, pages 644-649, XP002204039 compounds 7d,e	43
	-/-	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/09633

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S. EL-KOUSY ET AL.: "Synthesis and investigation of antiviral activity of 3'-O-(aminoalkyl)-thymidines and their quaternary ammonium salts" MONATSHEFTE FÜR CHEMIE, vol. 125, 1994, pages 713-721, XP002204040 compounds 4a-d, 6a-d -----	43
X	N.K. KOCHETKOV ET AL.: "The mechanism of the reaction of hydroxylamine and O-methylhydroxylamine with cytidine" TETRAHEDRON LETTERS, 1967, pages 3253-3257, XP002204041 compound 4a -----	47, 48
E	WO 01 90121 A (NOVIRIO PHARMACEUTICALS LTD ;UNI DEGLI STUDI DI CAGLIARI (IT); LAC) 29 November 2001 (2001-11-29) the whole document -----	1-57

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/09633

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 9401443	A	20-01-1994		AU 4508593 A CA 2139132 A1 CN 1087089 A EP 0648218 A1 WO 9401443 A1 JP 7508531 T MX 9303985 A1 ZA 9304742 A		31-01-1994 20-01-1994 25-05-1994 19-04-1995 20-01-1994 21-09-1995 28-02-1994 03-01-1995
WO 9816184	A	23-04-1998		AU 727177 B2 AU 4899997 A BR 9714349 A CA 2322053 A1 CA 2323791 A1 CN 1286258 A CN 1296011 A CN 1233254 A CZ 9901267 A3 EP 1072607 A2 EP 0961775 A2 HU 0001186 A2 JP 2001524936 T JP 2002105096 A NO 991784 A NO 20004326 A NO 20004328 A NZ 505531 A NZ 505553 A NZ 505554 A PL 332694 A1 SI 20024 A SK 48199 A3 US 2002058635 A1 WO 9816184 A2 AU 736075 B2 AU 6023898 A BR 9807473 A CN 1312254 A CN 1289594 A CN 1253504 T EP 1103559 A1 EP 0998293 A1 HU 0001526 A2 JP 2002515892 T JP 2002080490 A NO 993439 A NO 20004327 A NO 20004329 A PL 336579 A1 SI 9820003 A SK 94099 A3 WO 9830223 A1		07-12-2000 11-05-1998 14-11-2000 16-07-1998 23-04-1998 07-03-2001 23-05-2001 27-10-1999 14-07-1999 31-01-2001 08-12-1999 28-05-2001 04-12-2001 10-04-2002 15-06-1999 15-06-1999 15-06-1999 31-08-2001 30-11-2001 30-11-2001 27-09-1999 29-02-2000 18-01-2000 16-05-2002 23-04-1998 26-07-2001 03-08-1998 21-03-2000 12-09-2001 04-04-2001 17-05-2000 30-05-2001 10-05-2000 28-05-2001 28-05-2002 19-03-2002 13-09-1999 13-09-1999 13-09-1999 03-07-2000 30-06-1999 11-06-2001 16-07-1998
WO 9405687	A	17-03-1994		AU 4973393 A CA 2143834 A1 EP 0658166 A1 WO 9405687 A1 JP 8504753 T		29-03-1994 17-03-1994 21-06-1995 17-03-1994 21-05-1996

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/09633

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
EP 0468352	A	29-01-1992	AU AU CA CN EP JP US	642031 B2 8125391 A 2047644 A1 1059524 A ,B 0468352 A2 5001044 A 5374625 A		07-10-1993 30-01-1992 25-01-1992 18-03-1992 29-01-1992 08-01-1993 20-12-1994
US 5102873	A	07-04-1992	NONE			
US 4755594	A	05-07-1988	AU AU CA DK EP FI KR NO NZ PH PT JP ZA	592728 B2 6797287 A 1270821 A1 46687 A 0232813 A2 870371 A 9100602 B1 870390 A ,B, 219128 A 23342 A 84226 A ,B 62228095 A 8700120 A		18-01-1990 06-08-1987 26-06-1990 01-08-1987 19-08-1987 01-08-1987 28-01-1991 03-08-1987 29-01-1990 14-07-1989 01-02-1987 06-10-1987 31-08-1988
US 5998387	A	07-12-1999	US US US AU AU BR CA EP JP NZ NZ WO US AT AU AU CA DE DE DK EP ES GR JP JP PT WO	5736528 A 5631260 A 5446046 A 728439 B2 1522097 A 9612324 A 2238736 A1 1019426 A1 2000502712 T 326608 A 502628 A 9724363 A1 5668139 A 187726 T 699630 B2 1044995 A 2172726 A1 69422191 D1 69422191 T2 725782 T3 0725782 A1 2141913 T3 3032730 T3 9507052 T 2002105094 A 725782 T 9511904 A1		07-04-1998 20-05-1997 29-08-1995 11-01-2001 28-07-1997 28-12-1999 10-07-1997 19-07-2000 07-03-2000 28-04-2000 29-06-2001 10-07-1997 16-09-1997 15-01-2000 10-12-1998 22-05-1995 04-05-1995 20-01-2000 25-05-2000 13-06-2000 14-08-1996 01-04-2000 30-06-2000 15-07-1997 10-04-2002 31-05-2000 04-05-1995
US 3891623	A	24-06-1975	DE BE CH CS FR GB	2122991 A1 783026 A1 579585 A5 171723 B2 2135249 A5 1395764 A		16-11-1972 06-11-1972 15-09-1976 29-10-1976 15-12-1972 29-05-1975

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/09633

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
US 3891623	A		NL	7206058 A	07-11-1972
US 4526988	A	02-07-1985	AT	29726 T	15-10-1987
			AU	565856 B2	01-10-1987
			AU	2537484 A	13-09-1984
			BG	40814 A3	16-02-1987
			CA	1218647 A1	03-03-1987
			CA	1223869 C	07-07-1987
			CS	246075 B2	16-10-1986
			CY	1489 A	08-12-1989
			DD	216468 A5	12-12-1984
			DE	3466224 D1	22-10-1987
			DK	114484 A , B,	11-09-1984
			DK	190590 A	10-08-1990
			EP	0122707 A1	24-10-1984
			ES	530364 D0	01-12-1985
			FI	840890 A , B,	11-09-1984
			GB	2136425 A , B	19-09-1984
			GB	2172287 A , B	17-09-1986
			GR	81845 A1	12-12-1984
			HK	44989 A	09-06-1989
			HU	193893 B	28-12-1987
			IE	57071 B1	22-04-1992
			IL	71143 A	31-07-1988
			IL	80463 A	31-07-1988
			JP	1986188 C	08-11-1995
			JP	6009602 A	18-01-1994
			JP	6102655 B	14-12-1994
			JP	1833350 C	29-03-1994
			JP	5042438 B	28-06-1993
			JP	59175498 A	04-10-1984
			KE	3874 A	30-06-1989
			KR	8601283 B1	05-09-1986
			LU	88791 A9	05-11-1996
			MX	9203246 A1	31-07-1992
			NZ	207358 A	06-03-1987
			PH	23240 A	06-06-1989
			PH	23593 A	11-09-1989
			PL	246601 A1	13-08-1985
			PT	78181 A , B	01-04-1984
			RO	89963 A1	30-09-1986
			SG	21889 G	14-07-1989
			SU	1442076 A3	30-11-1988
			US	4808614 A	28-02-1989
			US	5015743 A	14-05-1991
			US	5118820 A	02-06-1992
			US	4692434 A	08-09-1987
			ZA	8401605 A	30-10-1985
WO 0190121	A	29-11-2001	AU	7490601 A	03-12-2001
			WO	0190121 A2	29-11-2001